CLAIMS

What is claimed is:

1. A method of producing a non-human mammal, referred to as an ES non-human mammal, wherein pluripotent cells are introduced into tetraploid blastocysts of the same mammalian species under conditions that result in production of an embryo and the resulting embryo is transferred into a foster mother which is maintained under conditions that result in development of live offspring, wherein the pluripotent cells are non-inbred pluripotent cells

2. The method of claim 1, wherein the non-human mammal is a mouse.

3. The method of claim 2, wherein the pluripotent cells are embryonic stem cells and are introduced into tetraploid blastocysts by injection.

4. The method of claim 3, wherein injection is piezo microinjection.

5. A method of producing a non-human mammalian embryo comprising injecting non-human non-inbred ES cells into non-human tetraploid blastocysts and maintaining the resulting tetraploid blastocysts under conditions that result in formation of embryos, thereby producing a non-human mammalian embryo.

6. The method of claim 5, wherein the non-human non-inbred ES cells are mouse cells and the non-human mammalian embryo is a mouse.

7. The method of claim 6, wherein mutant mouse non-inbred ES cells are injected into non-human tetraploid blastocysts by piezo microinjection.

8. A non-human mammal produced by the method of claim 1.

9. A mouse produced by the method of claim 2.

10. A mouse produced by the method of claim 3.

11. A non-human mammalian embryo produced by the method of claim 5.

12. A mouse embryo produced by the method of claim 6.

13. A mouse embryo produced by the method of claim 7.

14. A method of producing a mutant non-human mammal, wherein pluripotent cells comprising at least one mutation in genomic DNA are introduced into tetraploid blastocysts of the same mammalian species under conditions that result in production of an embryo and the resulting embryo is transferred into a foster mother which is maintained under conditions that result in development of live offspring, thereby producing a mutant non-human mammal, wherein the pluripotent cells are non-inbred pluripotent cells.

15. The method of claim 14, wherein the non-human mammal is a mouse.

16. The method of claim 15, wherein the pluripotent cells are embryonic stem cells and are introduced into tetraploid blastocysts by injection.

17. The method of claim 16, wherein injection is piezo microinjection.

18. A method of producing a mutant non-human mammalian embryo comprising injecting mutant non-human non-inbred ES cells into non-human tetraploid blastocysts and maintaining the resulting tetraploid blastocysts under conditions that result in formation of embryos, thereby producing a mutant non-human mammalian embryo.

19. The method of claim 18, wherein the mutant non-human non-inbred ES cells are mouse cells and the mutant non-human mammal is a mouse.

20. The method of claim 19, wherein mutant mouse non-inbred ES cells are injected into non-human tetraploid blastocysts by piezo microinjection.

21. A mutant non-human mammal produced by the method of claim 14.

22. A mutant mouse produced by the method of claim 15.

23. A mutant mouse produced by the method of claim 16.

24. A mutant mouse embryo produced by the method of claim 17.

25. A mutant mouse embryo produced by the method of claim 19.

26. A mutant mouse embryo produced by the method of claim 20.

27. A method of producing a mutant mouse, comprising: (a) introducing mouse non-inbred ES cells comprising at least one mutation in genomic DNA into mouse tetraploid blastocysts, thereby producing mouse blastocysts containing mouse non-inbred ES cells; (b) maintaining the product of (a) under conditions that result in production of embryos; (c) introducing an embryo into a pseudopregnant female: and (d) maintaining the female into which the embryo is introduced under conditions that result in development of live offspring, thereby producing a mutant mouse.

28. The method of claim 27, wherein in (a) introducing is carried out by injection.

29. The method of claim 28, wherein microinjection is piezo microinjection.

30. The method of claim 29, wherein the at least one mutation in genomic DNA is a gene knockout or exogenous DNA incorporated into the genomic DNA.

31. A mouse embryo produced from a mouse tetraploid blastocyst having incorporated therein mutant mouse non-inbred ES cells.

32. The mouse embryo of claim 31, wherein the non-inbred ES cells are selected from the group consisting of: V6.5 cells; 129B6 cells; F1.2-3 cells; V8.1 cells; V17.2 cells and V30.11 cells.

33. The mouse embryo of claim 31, wherein the mutant mouse non-inbred ES cells comprise at least one mutation selected from the group consisting of: transgenes which are cDNA, genes or portions thereof; targeted mutations, random mutations, conditional mutations, targeted insertions of foreign genes, YAC

sized transgenes, BAC sized transgenes, and all or part of a chromosome.

34. The mouse embryo of claim 33, wherein the at least one alteration in genomic DNA is a gene knockout or exogenous DNA incorporated into the genomic DNA.

35. A method of producing a mouse, comprising: (a) introducing mouse non-inbred ES cells into mouse tetraploid blastocysts, thereby producing mouse blastocysts containing mouse non-inbred ES cells; (b) maintaining the product of (a) under conditions that result in production of embryos; (c) introducing an embryo into a pseudopregnant female: and (d) maintaining the female into which the embryo is introduced under conditions that result in development of live offspring, thereby producing a mouse.

36. The method of claim 35, wherein in (a) introducing is carried out by injection.

37. The method of claim 36, wherein microinjection is piezo microinjection.

38. A mouse embryo produced from a mouse tetraploid blastocyst having incorporated therein mouse non-inbred ES cells.

39. The mouse embryo of claim 38, wherein the non-inbred ES cells are selected from the group consisting of: V6.5 cells; 129B6 cells; F1.2-3 cells; V8.1 cells; V17.2 cells and V30.11 cells.

40. A method of identifying a drug to be administered to treat a condition in a mammal in which the condition occurs, comprising producing, using the method

of claim 14, a mutant mouse that is a model of the condition; administering to the mutant mouse a drug to be assessed for its effectiveness in treating or preventing the condition; assessing the ability of the drug to treat or prevent the condition, wherein if the drug reduces the extent to which the condition is present or progresses, the drug is a drug to be administered to treat the condition.

41. A method of producing a mutant non-human mammal, mammal, wherein pluripotent cells comprising at least one mutation in genomic DNAare introduced into tetraploid blastocysts of the same mammalian species under conditions that result in production of an embryo and the resulting embryo is transferred into a foster mother which is maintained under conditions that result in development of live offspring, wherein the pluripotent cells are non-inbred pluripotent cells

42. A method of producing a mutant mouse that is derived from a single non-inbred ES cell clone, comprising breeding a mutant male mouse and a mutant female mouse, wherein the male mouse and the female mouse or an ancestor thereof were produced from the same non-inbred male ES cell and the female mouse is an XO female.

43. The method of claim 42, wherein the non-inbred cell clone is a non-inbred F1 cell clone.

44. A method of producing XO F1 ES cells, comprising introducing into male F1 ES cells a negative selection marker, under conditions appropriate for insertion of the negative selection marker in the Y chromosome of male F1 ES cells, thereby producing a mixture of male F1 Es cells comprising male F1 ES cells in which

the negative selection marker in inserted in the Y chromosome and other male F1 ES cells, some of which do not contain a Y chromosome; subjecting the resulting mixture to conditions that result in the death of male F1 ES cells in which the Y chromosome has the negative selection marker inserted therein and do not result in the death of male F1 ES cells that lack a Y chromosome and are XO F1 ES cells, thereby producing XO F1 ES cells.

45. An XO female mouse produced by introducing XO F1 ES cells into tetraploid mouse blastocysts under conditions that result in production of an embryo and transferring the resulting embryo into a foster mother which is maintained under conditions that result in development of live offspring, wherein the live offspring are XO female mice.

46. A method of producing a mutant mouse strain, comprising breeding a mutant male mouse and a mutant female mouse, wherein the mutant male mouse and the mutant female mouse or an ancestor thereof were derived from the same non-inbred male mouse ES cell clone and the mutant female mouse is an XO female.

47. The method of claim 46, wherein the non-inbred male ES cell is an F1 male mouse ES cell.

48. The method of claim 47, wherein the mutant XO female mouse or an ancestor thereof was derived from an male mouse F1 ES cell by knocking out the Y chromosome of the F1 ES cell, thereby producing an XO F1 ES cell; introducing the XO F1 ES cell into a tetraploid mouse blastocyst under conditions that result in production of an embryo and transferring the resulting

embryo into a foster mother which is maintained under conditions that result in development of live offspring, thereby producing an XO female offspring.